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Anti-tumour necrosis factor therapy for severe inflammatory arthritis:

Two years of experience in Northern Ireland

A P Cairns, A J Taggart

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SUMMARY

Etanercept and infliximab are novel biological agents targeted against tumour necrosis factor alpha (TNFα), a key cytokine in the pathogenesis of rheumatoid arthritis (RA). We report the results of their use over a two year period in 94 patients with severe inflammatory arthritis. Eighty-eight adults with active inflammatory arthritis (82 with RA), unresponsive to all conventional treatment, received biological therapy in one of five specialist centres in Northern Ireland. 69 adult patients (78%) had a good response to treatment, four a partial response, and seven no response. The results of treatment could not be assessed in eight patients because they had only recently commenced therapy. Four patients had a mild allergic reaction to treatment but one patient developed fulminant lung fibrosis which may have been due to drug therapy and eventually proved fatal. There were four cases of major infection requiring hospitalisation. Two patients responded to treatment, but one succumbed to bacterial pneumonia, and another to bacterial meningitis. Six children with juvenile idiopathic arthritis (JIA) received etanercept. Four achieved a good response, one a partial response, and one no response to treatment. This study shows that the impressive response to anti-TNF therapies extends beyond the realm of clinical trials to everyday clinical practice. These agents represent a major advance in the treatment of severe inflammatory arthritis but they should be used with caution, particularly in the elderly and in patients who are predisposed to infection.

INTRODUCTION

RA is a common disease (prevalence 0.5-1%),[1] with a tendency for ongoing inflammation, which may lead to progressive joint destruction, functional impairment and handicap. Spontaneous remissions are rare and it is now known that significant joint damage can occur within the first two years of disease onset.[2,3] Modern management strategies stress the importance of early diagnosis and treatment with disease modifying anti-rheumatic drugs (DMARDs), particularly methotrexate, which is now the "gold standard" by which other therapies are judged.[4] Despite this, a significant number of patients (around 10%) fail to respond to conventional DMARDs, either alone or in combination. Their disease follows a relentless downhill course with persistent joint inflammation and damage. RA of this severity carries a significant mortality[5] which is compounded by the need for regular corticosteroid therapy in order to achieve some quality of life.

The cytokine, TNFα, is produced by activated macrophages, and has a central role in the pathogenesis of RA with elevated TNFα levels found in affected Joints.[6] It is also implicated in a number of other inflammatory diseases including

Department of Rheumatology, Musgrave Park Hospital, Stockman's Lane, Belfast BT9 7JB.

A P Cairns, MD, MRCP, Specialist Registrar in Rheumatology

A J Taggart, MD, FRCP, Consultant Rheumatologist

Correspondence to Dr Cairns

ankylosing spondylitis, psoriatic arthritis, juvenile idiopathic arthritis, Behcet's and Crohn's disease. Infliximab and etanercept are the first of a new class of targeted modifiers of biological response to TNFα which have been licensed for use against intractable rheumatoid arthritis. Infliximab (*Remicade*) is a chimeric monoclonal antibody whilst Etanercept (*Enbrel*) is a soluble TNF receptor antagonist. Both drugs act to reduce the effective levels of intra-articular TNFα. Infliximab is administered by intravenous infusion every 6-8 weeks and is given concurrently with methotrexate (or azathioprine) to reduce the risk of allergic reaction to the chimeric protein. Etanercept is self-administered subcutaneously twice a week. Both drugs have been shown to be extremely effective in controlling active rheumatoid disease and retarding the progression of joint damage when compared with methotrexate,[7-9] and etanercept has also been shown to be effective in treating resistant JIA.[10]

The British Society for Rheumatology (BSR) has produced guidelines for the administration of these drugs in the UK.[11] To be considered for these therapies patients must have active RA as defined by the Disease Assessment Score (DAS) [12] – a validated composite score consisting of weighted swollen and tender joint counts, ESR, and patient functional visual analogue scale. They must also have failed on at least two conventional DMARDS (including full doses of methotrexate if tolerated). Contraindications to treatment include active infection, malignancy within the past 10 years, multiple sclerosis, severe heart failure, an indwelling catheter and chronic leg ulcers. There has been a trend towards the earlier use of these drugs, particularly in the USA, and increasing evidence suggests that they are effective in other inflammatory arthritides such as ankylosing spondylitis and psoriatic arthritis.[13, 14]

METHODS

Detailed records were kept of all patients receiving anti-TNF therapy (infliximab or etanercept) for inflammatory arthritis in Northern Ireland between November 1999 and October 2001. Response to treatment was assessed after three months as defined by BSR Guidelines for patients with peripheral joint disease (DAS score improved by > 1.2, or total DAS reduced to <3.2). Response in ankylosing spondylitis patients was assessed using ESR, CRP and BASDAI (Bath Ankylosing Spondylitis Disease Activity Index).[15] Patients were monitored at regular intervals throughout the study period for signs of adverse drug reaction or intercurrent illness.

RESULTS

88 adults (mean age 51 years, range 23-78; 65 female, 23 male) with inflammatory arthritis received treatment in five specialist centres. All had established, severe, active disease, unresponsive to multiple conventional therapies. 66 patients were treated in Musgrave Park Hospital, nine in Altnagelvin Area Hospital, five in Craigavon Area Hospital, five in Antrim Area Hospital, and three in the Ulster Hospital, Dundonald (fig. 1). 82 patients had RA, four ankylosing spondylitis, one psoriatic arthritis, and one persistent juvenile arthritis. 52 patients

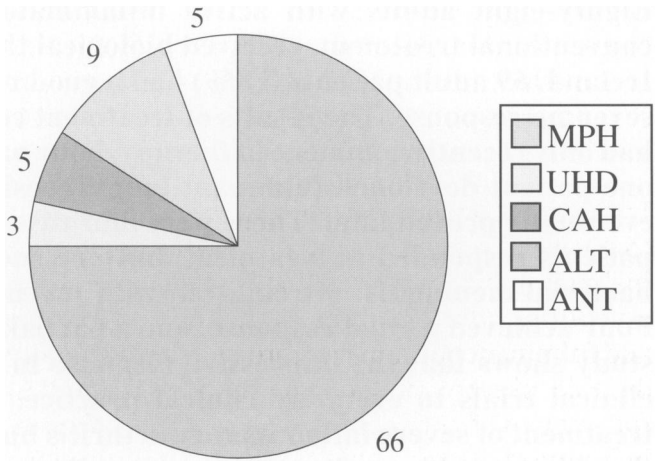

Fig 1. Adult treatment numbers by location (n=88; MPH=Musgrave Park Hospital, UHD=Ulster Hospital Dundonald, CAH=Craigavon Area Hospital, ALT=Altnagelvin Area Hospital, ANT=Antrim Area Hospital).

received infliximab (59%), and 36 etanercept (41%). 47 of the patients (53%) were taking concomitant oral corticosteroids. Six children (mean age 14, range 8-18, three male, three female) with JIA received etanercept, all in Musgrave Park Hospital.

63 of 82 (76%) patients with RA achieved a good response to treatment. Four (5%) had a partial response (i.e. met DAS response criteria but required intermittent intramuscular or intravenous steroid therapy) and seven (9%) did not respond. Eight patients (10%) had not been on treatment long enough (3 months) to be assessed (fig. 2). Both patients with psoriatic arthritis and persistent juvenile arthritis achieved a good response

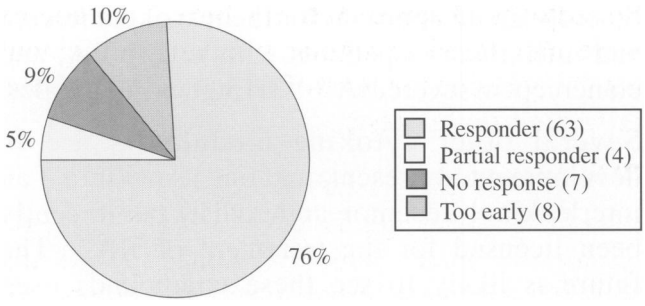

Fig 2. Response to anti-TNF therapies in adults with rheumatoid arthritis (n=82).

according to DAS scores and all patients with ankylosing spondylitis achieved a good response according to ESR, CRP and BASDAI scores. Overall, 78% of adults achieved a good response, 5% a partial response and 8% no response. 9% of patients could not be assessed because they had only recently commenced treatment. There was a trend towards higher response rates for infliximab and methotrexate (n=52, 42 (80%) responders) compared with etanercept monotherapy (n=36, 27 (75%) responders) in all adults.

In the adult group, four minor allergic reactions (5%) were reported. A fifth patient, receiving infliximab (with methotrexate), developed acute alveolitis, adult respiratory distress syndrome and fulminant pulmonary fibrosis. She eventually died despite treatment in an intensive care unit for seven weeks. There were four cases of major infection (5%), requiring hospital admission. One patient, on infliximab (with azathioprine, not on oral steroids), developed miliary tuberculosis. This was isolated from sputum and urine after 12 weeks of treatment.

Pre-treatment chest X-Ray had been normal, and there was no prior history or family history of tuberculosis. A second, on etanercept, developed probable septic arthritis in three joints, although an organism was not isolated as antibiotics had been given prior to joint aspiration. Both patients responded to appropriate antibiotic therapy. A third patient, on etanercept, developed a middle ear infection, which rapidly progressed to pneumococcal meningitis with brain abscess, and died after a protracted illness. A fourth patient, also on etanercept, developed a severe lobar pneumonia and died after a short illness. The mean age of patients with major infections was 65 years (range 53-76). 18 (20%) minor infections were recorded, during which biological treatment was temporarily discontinued.

Treatment was withdrawn in 18 of 88 adult patients (22%). The reasons for withdrawal were adverse events (nine patients), non-response (five patients), other (unrelated) illness (two patients), and other reasons (two patients) – one attempting to conceive, one concerned about potential adverse effects.

Six children with JIA received etanercept. Four achieved a good response to treatment, one a partial response and one no response. Treatment was temporarily withdrawn in the partial responder because of an episode of gastroenteritis.

DISCUSSION

In this cohort of 94 patients, at least 78% of adults and 67% of children with inflammatory arthritis achieved a good response to anti-TNF therapy as defined by BSR response criteria. Although the scoring systems used in Europe (DAS score) and North America (American College of Rheumatology (ACR) response criteria) differ slightly, these results compare favourably with large scale published trials where 42% to 59% of established RA patients receiving infliximab (with methotrexate) achieved an ACR 20 response (20% improvement in disease activity), and 72% of early rheumatoid arthritis patients receiving etanercept achieved an ACR 20 response after 12 months of treatment.[7-9] This confirms that the efficacy of anti-TNF therapies extends beyond trial conditions to everyday clinical practice. This was further emphasised by the fact that many of our patients were able to reduce or stop their oral corticosteroids. These drugs therefore represent a major advance in the treatment of inflammatory arthritis.

Both drugs were generally well tolerated with 80% of adults and 75% of children remaining on treatment at the end of the study period. This compares favourably with conventional DMARD therapies. Infections were common, with minor infection seen in one fifth of patients receiving these drugs. Serious infections occurred in 5% of our patients. Although this group of patients is prone to infectious complications by nature of their inflammatory condition, and use of DMARDS and corticosteroids,[5] it remains to be seen whether this serious infection rate is higher than would be seen in a group with similar characteristics, but not receiving anti-TNF therapy. Data from trial conditions would suggest that serious infection rates are similar in established RA patients receiving methotrexate

alone (8%), compared with those receiving methotrexate with infliximab (6%).[8] A major trial comparing etanercept alone with methotrexate alone in early RA found no difference in the rate of serious infections between the groups (both less than 3%).[9] The slightly lower serious infection rate in this study may be partly attributable to the fact that these patients had early, rather than established, rheumatoid disease. The BSR is compiling a registry on the use of anti-TNF drugs with control groups not receiving either drug, which should allow a more formal assessment of the relative risk of infectious disease attributable to anti-TNF therapy in clinical practice.[11]

In our study the average age of patients who developed serious infection was greater than in the cohort as a whole (65 versus 51 years) and this has led to even greater caution in the use of these drugs in older patients, particularly those with multiple co-morbidities. Serious infections occurred with both etanercept and infliximab, and seemed to progress rapidly. All patients receiving potent immunosuppressives should be educated about symptoms that might suggest infection and should be encouraged to report such symptoms to their doctor immediately and, in the case of etanercept, stop administering the drug until advice is received. All of our patients are instructed about the risks of sepsis before they start biological therapy and each is given an information card (similar to the well-known steroid card) to carry in the event of an emergency. This is particularly pertinent for patients self-administering etanercept, where we have noticed that a number of patients seem reluctant to stop temporarily their injections in the presence of minor infection, because of a worry about the loss of clinical effect.

The use of these drugs has significant resource implications. Each drug costs approximately £8000 per patient per year, and treatment must be continued long-term if it is to remain effective. The additional demands on medical and nursing staff must also be considered. Patient selection, drug administration and ongoing safety monitoring are all costly but essential parts of a biological treatment programme. Nevertheless, the benefits of these new therapies are such that these costs can be fully justified in terms of the potential prevention of long-term joint damage and disability. It is not surprising therefore, that the National Institute of Clinical Excellence has recently given approval for the use of etanercept and infliximab in patients with severe RA, and etanercept in severe JIA[16, 17] in England and Wales.

Several other cytokine modulators are in development at present, and one (Anakinra – an interleukin 1 receptor antagonist) has recently been licensed for the treatment of RA.[18] The future is likely to see these compounds used much earlier in the course of the disease and in various combinations. The ACR now recommends considering the use of biological agents if there is ongoing rheumatoid disease activity after three months of full dose methotrexate therapy.[19] Combinations of biological agents which work at different points in the inflammatory cascade may ultimately make the induction of disease remission a realistic prospect.

In conclusion, our experience in Northern Ireland over a two year period has confirmed that the anti-TNF therapies, etanercept and infliximab, represent a significant advance in the treatment of severe RA and JIA. They are also of benefit in other inflammatory arthritides such as psoriatic arthritis and ankylosing spondylitis. Adverse events in this cohort were not uncommon, and there were a number of serious infections in our patients (5%). These sometimes occurred rapidly and with little warning. We therefore recommend that these drugs be administered only in specialist centres to carefully selected patients. Our experience confirms the need for careful ongoing safety monitoring of these patients.

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